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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/749,601	12/28/2000	Nicholas C. Nicolaides	01107.00069	4817

22907 7590 12/02/2003

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EXAMINER	
KRUSE, DAVID H	

ART UNIT	PAPER NUMBER
1638	20

DATE MAILED: 12/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/749,601	NICOLAIDES ET AL.	
	Examin r	Art Unit	
	David H Kruse	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,22-35,37-77 and 79-125* is/are pending in the application.

4a) Of the above claim(s) *3,4,6-14,22-30,37-45,48-55,57-76,80-82 and 86-125* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,15,18-20,31,34,35,47,77,79 and 83* is/are rejected.

7)☒ Claim(s) *16, 17, 32, 33, 46, 56, 84 and 85* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. This Office action is in response to the Amendment and Remarks filed 12 June 2003.

2. Those rejections not specifically addressed in this Office action are withdrawn in view of Applicant's amendments and/or arguments.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

4. This application contains claims 3, 4, 6-14, 22-30, 37-45, 48-55, 57-76, 80-82 and 86-125 drawn to an invention nonelected with traverse in Paper No. 15, filed 27 November 2002. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR § 1.144). See MPEP § 821.01

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR § 1.48(b) and by the fee required under 37 CFR § 1.17(i).

Claim Rejections - 35 USC § 112

6. Claims 1, 2, 5, 15, 18-20, 31, 34, 35, 47, 77, 79 and 83 remain rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is repeated for the reason of record as set forth in the last Office action mailed 12 February 2003. Applicant's arguments filed 12 June 2003 have been fully considered but they are not persuasive.

Applicant argues that the specification or the prior art discloses the amino acid sequence of the human, mouse and Arabidopsis *PMS2*, that the *PMS2* gene of human and mouse are closely related and are representative of the recited genus of mammalian *PMS2* genes, and that the specification discloses that a truncation mutation of either the human or Arabidopsis *PMS2* genes results in a dominant negative *PMS2* protein (pages 14-15 of the Remarks). Applicant also argues that this mutation in the *PMS2* gene of human and Arabidopsis genes is very likely representative of the mutation of other mammalian *PMS2* alleles and thereby correlating function with a know particular structure (page 15, 2nd paragraph of the Remarks). These arguments are not found to be persuasive because at the time of Applicant's invention, only two mammalian *PMS2* encoding polynucleotides were know and thus one of skill in the art could not correlate structure to function of a polynucleotide encoding a full length *PMS2* protein. In addition, the instant claims are directed to any mutation or truncation mutation of a *PMS2* encoding polynucleotide that functions as a dominant negative allele. It is clear from the art as cited in the previous Office action that any truncation of an encoded *PMS2* protein does not produce to a dominant negative allele and thus

Applicant has not correlated structure and function for any truncation mutation as broadly claimed (see Pang *et al* 1997).

Applicant argues that the specification provides guidance for determining the mutations in the *PMS2* gene that result in dominant negative *PMS2* proteins and how to determine if a mutation of the *PMS2* gene causes the production of a dominant negative *PMS2* protein (page 15, 3rd paragraph of the Remarks). This argument is not found to be persuasive for the reasons given in the previous Office action. Essentially Applicant has only described how one of skill in the art might find other polynucleotides encoding a dominant negative *PMS2* allele. See *University of California V. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), which teaches that the disclosure of a process for obtaining cDNA from a particular organism and the description of the encoded protein fail to provide an adequate written description of the actual cDNA from that organism which would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism.

The rejection as directed to claims 17, 32, 33 and 85 is withdrawn (page 15, 4th paragraph of the Remarks).

7. Claims 1, 2, 5, 15, 18-20, 31, 34, 35, 47, 77, 79 and 83 remain rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of making a hypermutable plant cell comprising transforming said plant cell with a polynucleotide comprising nucleotide sequence that encodes the human *PMS2* 134 truncation mutation and plant cells and plants produced by said method, does not reasonably provide enablement for a method of making a hypermutable plant cell

comprising transforming said plant cell with a polynucleotide comprising any dominant negative allele of any mammalian *PMS2* and plant cells and plants produced by said method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection is repeated for the reason of record as set forth in the last Office action mailed 12 February 2003, and has been modified in view of Applicant's amendments to the claims. Applicant's arguments filed 12 June 2003 have been fully considered but they are not persuasive.

Applicant argues that the specification discloses a sufficient number of *PMS* genes containing dominant negative mutations for one of skill in the art to make and use the claimed invention without resorting to undue experimentation. Applicant argues that the specification discloses that the human and *A. thaliana* PMS134 genes share 53.2% nucleotide sequence identity and 65.1% and 50.7% amino acid sequence similarity and identity, respectively (paragraph spanning pages 8-9 of the Remarks). This argument is not found to be persuasive because the number of *PMS2* encoding polynucleotides taught by Applicant do not teach one of skill in the art at the time of Applicant's invention how to make and use polynucleotides from other mammals as broadly claimed. In addition, the Applicant does not teach one of skill in the art at the time of Applicant's invention how to make and use other truncation mutations or other dominant negative alleles of a mammalian *PMS2* as broadly claimed in claim 1, for example.

Applicant argues that the specification provides working examples of human and plant truncation mutations of *PMS2* each of which exerts a dominant negative effect

(page 9, 2nd paragraph of the Remarks). This argument is not found to be persuasive because the instant claims are directed to any dominant negative allele of a mammalian or human *PMS2* gene, wherein Applicant has only taught one example of a truncation mutation that functions to make a hypermutable plant cell.

Applicant argues that one of skill in the art would expect any mammalian *PMS2* gene to function similar to the taught human and plant *PMS2* genes (page 9, 3rd paragraph of the Remarks). This argument is not found to be persuasive for the reasons given above as directed to the breadth of the claimed invention.

Applicant argues that because the truncation of the human and plant *PMS2* genes produces a dominant negative phenotype in cells, one of skill in the art would have also have expected similar truncation mutations in other mammalian *PMS2* genes to have a similar effect (page 10, 1st paragraph of the Remarks). Again, this argument is not found to be persuasive for the reasons given above as directed to the breadth of the claimed invention.

Applicant argues that the specification provides guidance to aid in the selection of other dominant negative mutations that can be used in the claimed methods, cells or plants and that the specification discloses that a dominant negative *PMS2* gene may be a mutation that leads to a protein product which is able to complex with other members of the MMR complex but which is not functional. Applicant also argues that the specification provides sufficient disclosure of species of *PMS2* alleles, in conjunction with a structure/function relationship of the genes that exert a dominant-negative effect (page 10, 2nd paragraph of the Remark). This argument is not found to be persuasive

because it remains unclear from the teachings of the instant specification and that of the art as cited in the previous Office action that one of skill in the art can relate structure, a mutated and/or truncated *PMS2* protein, with function, functions as a dominant negative allele in a plant, because of the nature of the claimed invention.

Applicant argues that the teachings of Chang *et al* 2001 merely speculates that a mutation in *PMS2* may not result in loss of cellular MMR function or that if any loss is detected it is slight. Applicant agues that Chang *et al* 2001 does not teach that loss of *PMS2* function in a cell will result in no or only slight loss of MMR function (page 11 of the Remarks). This argument is not found to be persuasive because Applicant has only taught how to make and use the human *PMS134* mutation to make a hypermutable plant cell. Chang *et al* 2001 teaches the state of the art at the time of Applicant's invention, essentially that it was unpredictable. In addition, Applicant does not teach loss of *PMS2* function, but modification of MMR function in a transgenic plant cell, Applicant does not teach a deletion mutation of a plant *PMS2* gene.

Applicant argues that while Pang *et al* 1997 teach a single truncated *PMS2* protein that does not cause a dominant negative phenotype in yeast but they do teach several *PMS2* proteins that exert a dominant negative phenotype in yeast (paragraph spanning pages 11-12 of the Remarks). This argument is not found to be persuasive because what Pang *et al* 1997 teach is that one of skill in the art at the time of Applicant's invention cannot predict that any mutation or truncation of a *PMS2* gene will produce a dominant negative allele effect with out empirical evidence. Applicant teaches that the human *PMS2* protein has 862 amino acids, thus the instant claims

encompass at least 862 variants of a truncation mutation of only the human *PMS2* protein, of which Applicant has only taught how to make and use one.

The rejection as directed to claims 17, 32, 33 and 85 is withdrawn (page 12, 2nd paragraph of the Remarks).

Allowable Subject Matter

8. Claims 16, 17, 32, 33, 46, 56, 84 and 85 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. The claims under examination are free of the prior art which neither teaches nor fairly suggests a method of making a hypermutable plant cell comprising transforming

said plant cell with a polynucleotide encoding a dominant negative allele of a mammalian *PMS2* gene as claimed by Applicant.

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David H. Kruse, Ph.D. whose telephone number is (703) 306-4539, **(571) 272-0799 after 6 January 2004**. The examiner can normally be reached on Monday to Friday from 8:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Amy Nelson can be reached at (703) 306-3218, **(571) 272-0804 after 6 January 2004**. The fax telephone number for this Group is (703) 872-9306 Before Final or (703) 872-9307 After Final.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group Receptionist whose telephone number is (703) 308-0196.

AMY J. NELSON, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

David H. Kruse, Ph.D.
25 November 2003